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A Study on the Mechanism of Action of Galangal in the Treatment of Gastric Cancer Using Network Pharmacology Technology

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Abstract: To study the mechanism of galangal in the treatment of gastric cancer by network pharmacology. The TCMSP database was used to collect the effective compounds and potential targets of galangal, and the genes associated with gastric cancer were obtained through the GeneCards database, and Venn obtained the interaction genes of the effective compound targets of galangal and gastric cancer targets, plotted the interaction genes into PPI networks, and screened out key targets. The interacting genes were imported into Metascape database for GO enrichment analysis and KEGG signal enrichment. A total of 13 active compounds and 207 potential downstream target genes were screened by TCMSP database. Have 5222 gastric cancer target genes through GeneCards database, there were a total of 150 interactive genes and 6 key genes: TP53, AKT1, JUN, HSP90AA1, IL6, and CASP3. These interacting genes involved 30 typical GO entries and 20 KEGG signals. Galangal may play a role in the treatment of gastric cancer by means of multi-component, multi-target and multi-signal pathway.

Keywords: network pharmacology; galangal; gastric cancer

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1. Introduction

Gastric cancer (GC) is a common malignant tumor of digestive tract, and its morbidity and lethality rank among the top among all malignant tumors, and it is one of the malignant tumors that endanger human health. Gastric cancer ranks fifth in the global cancer incidence spectrum and fourth in the death cause spectrum. At present, 43.9% of new gastric cancer cases and 48.6% of gastric cancer deaths in the world occurred in China, both of which were slightly lower than the data in 2018, but still higher than the data in GLOBOCAN 2012. In the spectrum of incidence, gastric cancer still ranks third in China, but in the spectrum of causes of death, it has dropped by one place compared with 2018, ranking third [1].

In recent years, it has been found that galangal and some other Chinese herbal medicines are helpful for the treatment of gastric cancer. Galangal is the rhizome of the ginger plant, which has the functions of warming the stomach, dispelling wind and dispelling cold, and relieving pain. Indications of spleen and stomach cold, vomiting and diarrhea, nausea, loss of appetite [2]. Galangal mainly contains flavonoids [3], volatile oil [4] and diaryl heptane compounds [5], which are found to have antioxidant [6], hypoglycemic [7], antibacterial [8] and anti-ulcer effects [9], as well as certain anti-cancer effects. In recent years, many scholars have conducted in-depth research on galangal and found that galangin can induce tumor cell apoptosis [10], promote tumor cell autophagy [11], inhibits tumor cell metastasis [12] and other methods to achieve anti-tumor effect. In addition, Guzalinur Maitissa et al. studied the mechanism of galangal on cervical cancer cells [13], Xu Yunxia et al. studied the in vitro effect of galangal on human gastric cancer cells [14], Liu Zheng et al. studied the apoptotic effect of galangal on liver cancer cells [15], and Zou Wenwei et al. studied the mechanism of galangal on retinoblastoma [16]. Studies have shown that galangin has an inhibitory effect on human gastric cancer cells [17], which

may be achieved through various mechanisms, such as induction of apoptosis, cycle arrest and differentiation [18].

Network pharmacology is a discipline based on the construction of disease-phenotype-gene-drug multi-layer network, which can predict drug targets from a holistic perspective and improve the efficiency of drug discovery. In this study, the potential mechanism of action of galangal in the treatment of gastric cancer was predicted by network pharmacology method, and the mechanism of action of galangal in the treatment of gastric cancer based on TP53 and JUN pathway was further explored by molecular docking technology, so as to provide a reference for the subsequent experimental research of galangal.

2. Materials and Methods

2.1. Mining and Screening of Effective Compounds and Their Targets in Galangal

Using TCMSP [19] (Traditional Chinese Medicine Systems Pharmacology Database and Analysis Platform; http://lsp.nwu.edu.cn/tcmsp.php; accessed on 13 July 2022) screening for effective compounds of galangal (set oral bioavailability (OB) $\geq$ 30%, drug-like (DL) $\geq$ 0.18) to predict target genes corresponding to the corresponding effective compounds. In general, the general standard for active ingredient screening are OB (Oral bioavailability) $\geq$30%, DL (Drug-like properties) $\geq$ 0.18. The higher the OB and DL, the better the oral utilization and drug class, according to the amount of ingredients obtained by screening, the standard setting can also be appropriately adjusted, if the route of administration of the drug is not oral administration, the OB value is not considered, because OB is the content of the reaction drug absorbed into the blood through the gastrointestinal tract, such as intravenous administration, subcutaneous administration, mucosal administration and other ways without passing through the gastrointestinal tract, do not need to consider the OB value. In addition, the main active ingredient of galangal obtained through literature search and experiments can be exempted from the OB and DL values. All GENE names are converted into "GENE SYMBOL" through STRING database (https://string-db.org/; accessed on 13 July 2022) to search the interaction relationship of proteins.

2.2. Screening Genes Related to Gastric Cancer

Using GeneCards database (https://www.genecards.org/; accessed on 13 July 2022), screening of gastric cancer related gene set SCORE > 2 for the standard screen target genes of gastric carcinoma. SCORE represents the relevance of the target to the disease, and the higher the score, the higher the correlation with the disease. The median or average value is used as the threshold, and the genes above the threshold are screened out to be related genes for the disease. The threshold is too large, the number of genes obtained by screening is small, the threshold is too small, and the number of genes with low correlation between disease and target is large. The threshold setting > 2 to screen out genes with a large degree of correlation and the number of genes will not be too small.

2.3. Construction of "Compound-Interactive Gene" Network of Galangal

Through Venny (https://bioinfogp.cnb.csic.es/tools/venny/index.html; accessed on 13 July 2022) to produce effective compound galangal target genes and stomach cancer target genes Venn diagram, and through the Venn diagram to find interactive genes, Cytoscape was used to construct the network analysis diagram of compound-interaction genes. Cytoscape, based on Java, can be used to construct gene expression regulation or protein interaction networks [20].

3. Results

3.1. Basic Information of Effective Compounds in Galangal

The effective compounds of galangal were mined and screened by TCMSP database. According to the set OB and DL values, a total of 13 effective compounds were screened, as shown in Table 1.

Table 1. Information of 13 effective compounds in Galangal.

Mol ID	Molecule Name	OB (%)	DL
MOL001771	poriferast-5-en-3beta-ol	36.91	0.75
MOL002543	(2S,3R)-2-(3,4-dimethoxyphenyl)-5,7-dimethoxychroman-3-ol	51.89	0.37
MOL002544	1,7-diphenyl-5-hydroxy-3-heptanone	61.9	0.18
MOL002554	5-methoxy-1,7-diphenyl-3-heptanone	68.29	0.2
MOL002556	7-Methoxy-8-(2′-ethoxy-3′-hydroxy-3′-methybutyl)coumarin	40.36	0.21
MOL002563	galangin	45.55	0.21
MOL002565	Medicarpin	49.22	0.34
MOL002575	butyl-2-ethylhexyl phthalate	44.52	0.22
MOL000354	isorhamnetin	49.6	0.31
MOL000358	beta-sitosterol	36.91	0.75
MOL000359	sitosterol	36.91	0.75
MOL000422	kaempferol	41.88	0.24
MOL000098	quercetin	46.43	0.28

OB: oral bioavailability, DL: drug likeness.

3.2. *Venn Analysis of Effective Compound Targets of Galangal and Target Genes of Gastric Cancer*

Through the TCMSP database (http://lsp.nwu.edu.cn/tcmsp.php; accessed on 13 July 2022), 13 effective compounds of galangal were predicted to act on the target genes, and the target gene names were converted into "GENE SYMBOL" using the STRING database (https://string-db.org/; accessed on 13 July 2022), and 207 target genes were obtained. The target genes of gastric cancer-related diseases were screened through the GeneCards database (https://www.genecards.org/; accessed on 13 July 2022) [21], and 5222 gastric cancer target genes were screened with SCOR > 2 as the parameter standard. A total of 150 interacting genes were obtained by Venn analysis, as shown in Figure 1.

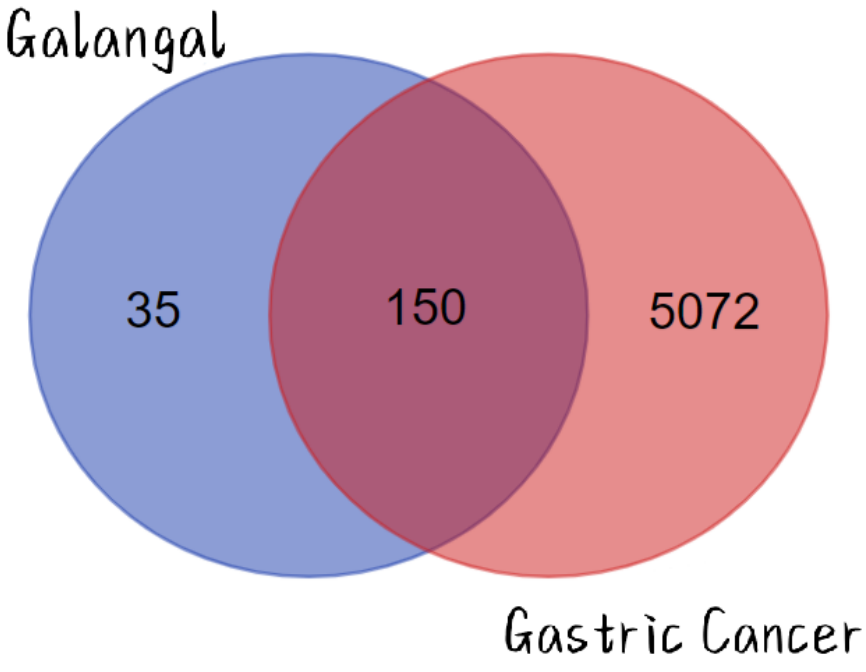

Figure 1. Venn diagram of the effective compounds of galangal and the target genes of gastric cancer.

3.3. Galangal-Component-Target-Gastric Cancer Network Construction

Cytoscape was used to construct the network analysis diagram of "compound-interaction genes". Quercetin, Kaempferol, Isorhamnetin, etc. had the most interaction genes in the network, as shown in Figure 2. These effective compounds which interact with interacting genes may provide important material basis for the anticancer effect of Galangal.

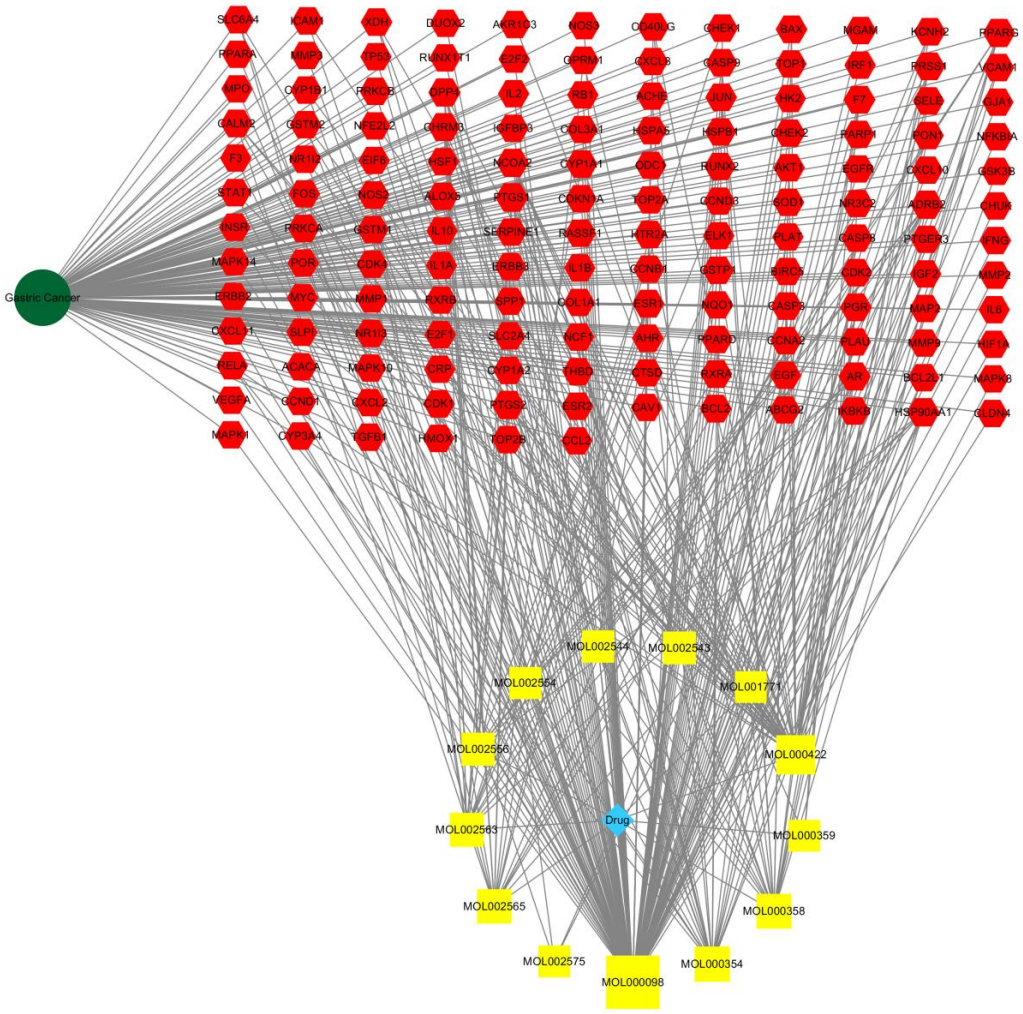

Figure 2. Galangal-component-target-gastric cancer network construction diagram. Blue: Drugs; Yellow: Active Ingredient ID; Green: Gastric Cancer; Red: Interactive target. Edge: The degree of association of the disease target with the drug component.

The results of network topology analysis show that the top 5 active ingredients of galangal anti-gastric cancer efficacy value are MOL000098, MOL000422, MOL000354, MOL000358 and MOL002565. The top 5 targets were PTGS2, PTGS1, ADRB2, HSP90AA1, and NCOA2, which fully demonstrated that galangal is an anti-gastric cancer effect through multi-component, multi-target, and multi-pathway synergistic mechanisms.

3.4. PPI Network Construction

150 interacting genes were input into the "Multiple Proteins" module of STRING database (https://string-db.org/; accessed on 13 July 2022), and confidence scores > 0.7 were set. After the proteins of interacting genes were retrieved, Cytoscape 3.6.0 software(California, USA, 2018) was used to display the PPI network, as shown in Figure 3. Using CytoHubba module (Cytoscape3.6.0software: California, USA, 2018)analysis, select six key node gene, TP53, AKT1, JUN, HSP90AA1, IL6, CASP3.

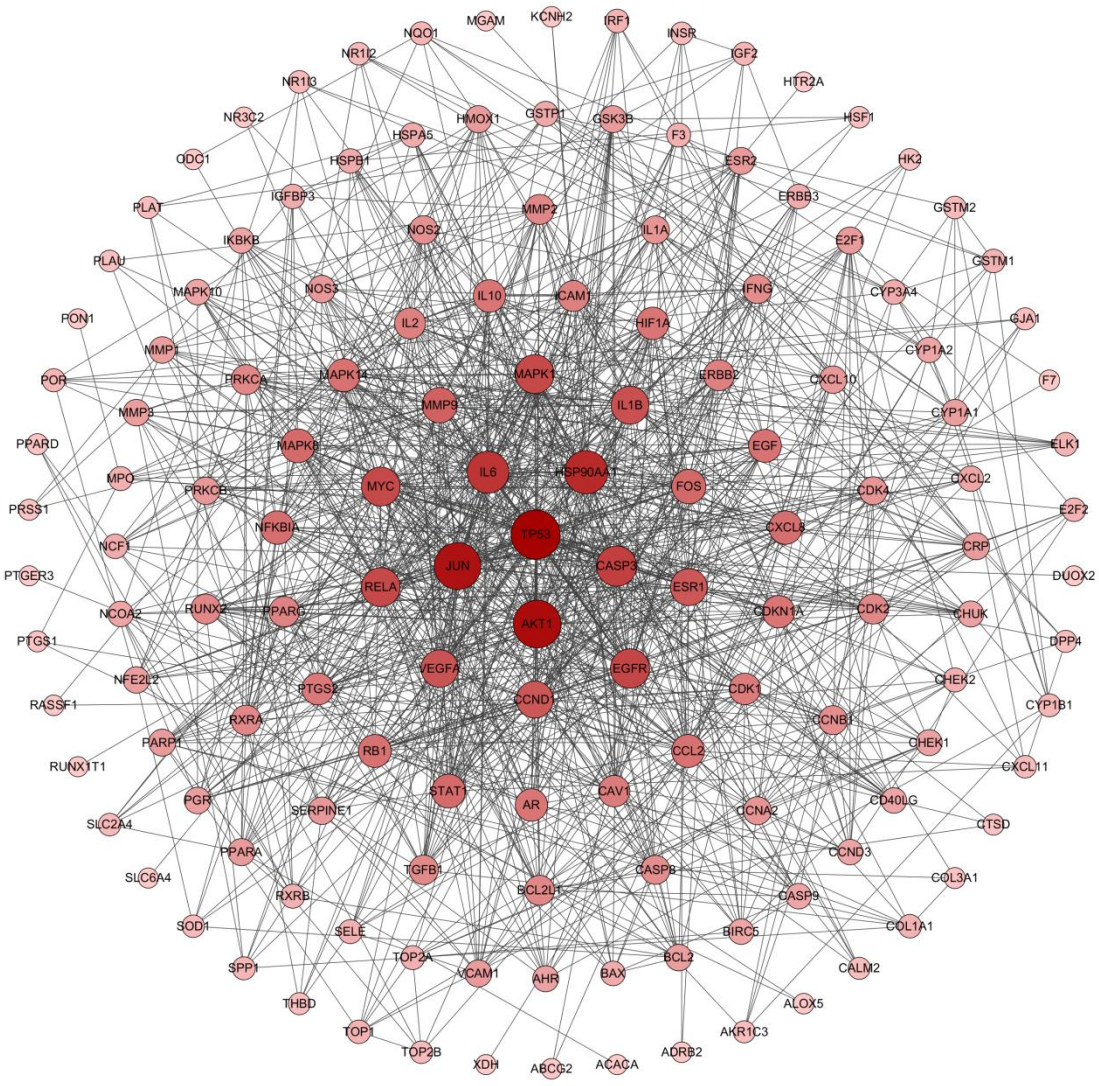

Figure 3. PPI network diagram. The darker the color, the higher the association of proteins with disease Edge: Represents the association between proteins.

3.5. GO Enrichment Analysis Results

150 interactive genes were fed into the Metascape database (http://metascape.org/gp/index.html/; accessed on 14 July 2022) for GO enrichment analysis. GO enrichment analysis mainly includes molecular function (MF), biological process (BP) and cellular component (CC) three parts. GO enrichment analysis results MF include DNA-binding transcription factor binding, kinase binding, nuclear receptor activity, protein domain specific binding, BP including response to hormone, cellular response to lipid, response to inorganic substance, response to xenobiotic stimulus, CC includes membrane raft, transcription regulator complex, protein kinase complex, vesicle lumen (Table 2). According to the number of genes, the top 10 entries were selected to draw a histogram (Figure 4).

3.6. KEGG Enrichment Analysis

The results of KEGG enrichment analysis showed that the signaling pathways of galangal acting on gastric cancer mainly included "Pathways in cancer", "Lipid and atherosclerosis", "AGE-RAGE signaling pathway in diabetic complications", "Hepatitis B", "Chemical carcinogenesis-receptor activation", "MAPK signaling pathway" as shown in Table 3. And make a KEGG channel enrichment analysis diagram, as shown in Figure 5.

Table 2. GO enrichment analysis.

Classification	Pathway	Count	%	Log10 (*p*)	Log10 (q)
TOP10 MF	GO:0140297:DNA-binding transcription factor binding	30	20	−23.91	−20.22
	GO:0019900:kinase binding	31	20.67	−19.09	−16
	GO:0004879:nuclear receptor activity	13	8.67	−18.45	−15.56
	GO:0019904:protein domain specific binding	28	18.67	−17.1	−14.32
	GO:0042803:protein homodimerization activity	27	18	−16.2	−13.47
	GO:0004672:protein kinase activity	24	16	−15.06	−12.42
	GO:0044389:ubiquitin-like protein ligase binding	18	12	−13.47	−10.94
	GO:0005126:cytokine receptor binding	17	11.33	−13.45	−10.94
	GO:0019207:kinase regulator activity	16	10.67	−13.23	−10.75
	GO:0020037:heme binding	11	7.33	−9.95	−7.74
TOP10 BP	GO:0009725:response to hormone	52	34.67	−44.57	−40.67
	GO:0071396:cellular response to lipid	46	30.67	−44.56	−40.67
	GO:0010035:response to inorganic substance	44	29.33	−41.13	−37.54
	GO:0009410:response to xenobiotic stimulus	39	26	−38.39	−34.98
	GO:0032496:response to lipopolysaccharide	35	23.33	−36.24	−32.95
	GO:0009991:response to extracellular stimulus	35	23.33	−30.27	−27.26
	GO:0009314:response to radiation	34	22.67	−30.22	−27.23
	GO:0070482:response to oxygen levels	30	20	−29.29	−26.36
	GO:0051272:positive regulation of cellular component movement	37	24.67	−29.19	−26.28
	GO:0048545:response to steroid hormone	28	18.67	−28.03	−25.21
TOP10 CC	GO:0045121:membrane raft	20	13.33	−15.58	−12.68
	GO:0005667:transcription regulator complex	23	15.33	−15.49	−12.68
	GO:1902911:protein kinase complex	12	8	−12.24	−9.56
	GO:0031983:vesicle lumen	14	9.33	−8.96	−6.52
	GO:0031012:extracellular matrix	16	10.67	−7.57	−5.42
	GO:0098797:plasma membrane protein complex	17	11.33	−7.05	−4.94
	GO:1905286:serine-type peptidase complex	4	2.67	−6.73	−4.67
	GO:0097180:serine protease inhibitor complex	3	2	−5.62	−3.62
	GO:0048471:perinuclear region of cytoplasm	15	10	−5.49	−3.55
	GO:0005819:spindle	11	7.33	−5.24	−3.33

Table 3. KEGG pathway enrichment.

KEGG Signaling Pathway	Count	%	Log10 (*p*)	Log10 (q)
hsa05200:Pathways in cancer	67	44.67	−76.4	−73.86
hsa05417:Lipid and atherosclerosis	42	28	−54.83	−52.6
hsa04933:AGE-RAGE signaling pathway in diabetic complications	32	21.33	−49.23	−47.17
hsa05161:Hepatitis B	33	22	−43.44	−41.6
hsa05207:Chemical carcinogenesis-receptor activation	34	22.67	−40.97	−39.21
hsa04010:MAPK signaling pathway	27	18	−25.67	−24.61
hsa05205:Proteoglycans in cancer	24	16	−25.37	−24.33
hsa01524:Platinum drug resistance	17	11.33	−23.43	−22.48
hsa04068:FoxO signaling pathway	18	12	−20.36	−19.53
hsa05202:Transcriptional misregulation in cancer	20	13.33	−20.13	−19.31
hsa04064:NF-kappa B signaling pathway	16	10.67	−18.96	−18.19
hsa04915:Estrogen signaling pathway	17	11.33	−18.41	−17.67

Table 3. *Cont.*

KEGG Signaling Pathway	Count	%	Log10 (*p*)	Log10 (q)
hsa05323:Rheumatoid arthritis	14	9.33	−16.5	−15.82
hsa04919:Thyroid hormone signaling pathway	15	10	−16.34	−15.66
hsa05144:Malaria	11	7.33	−15.01	−14.36
hsa05221:Acute myeloid leukemia	11	7.33	−13.5	−12.88
hsa04630:JAK-STAT signaling pathway	14	9.33	−13.06	−12.47
hsa04370:VEGF signaling pathway	10	6.67	−12.46	−11.9
hsa04914:Progesterone-mediated oocyte maturation	11	7.33	−11.42	−10.88
hsa04020:Calcium signaling pathway	14	9.33	−10.73	−10.2

3.7. Molecular Docking

Quercetin and kaempferol, which are highly correlated with gastric cancer disease, were selected from galangal to be molecularly docked with the proteins TP53 and JUN with a relatively large correlation of gastric cancer to verify the effect of the main active compounds on disease-related proteins, show in Table 4. Molecular docking is to make these two chemical components and proteins effectively docked together, into the human body to play a role in the disease. When the binding energy is less than 0, it indicates that the ligand and the receptor can bind on their own, and the greater the absolute value of the binding energy, the stronger the binding capacity. The binding energy of quercetin, kaempferol and TP53 and JUN is less than 0. The molecular docking diagram is shown in Figures 6–9.

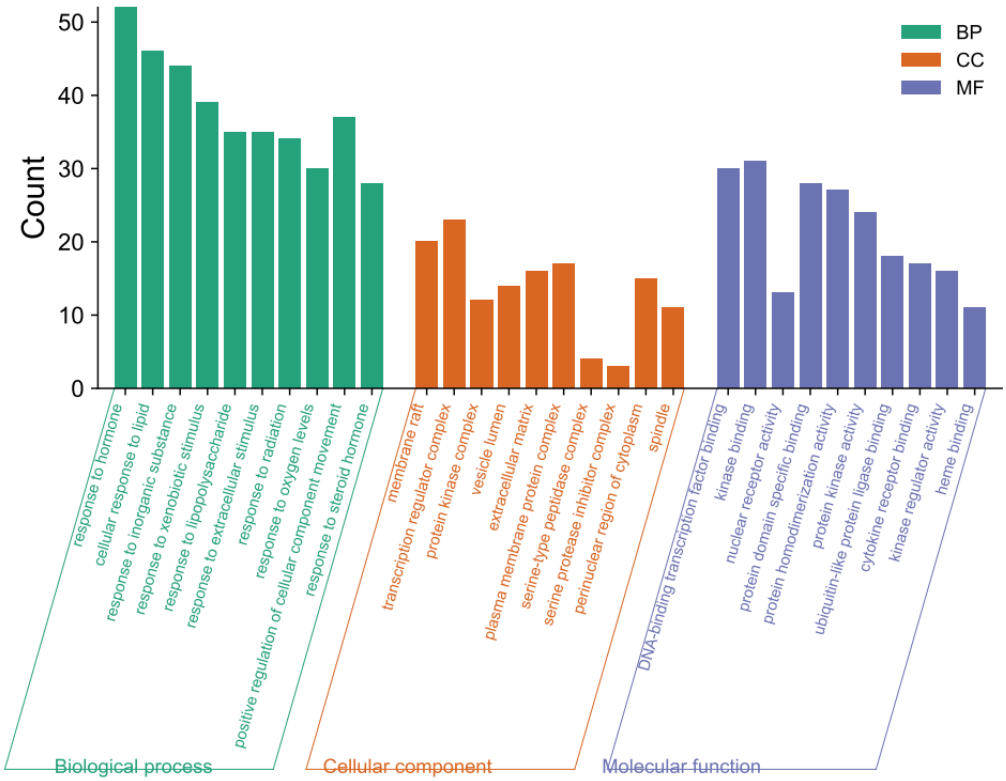

Figure 4. GO enrichment analysis diagram.

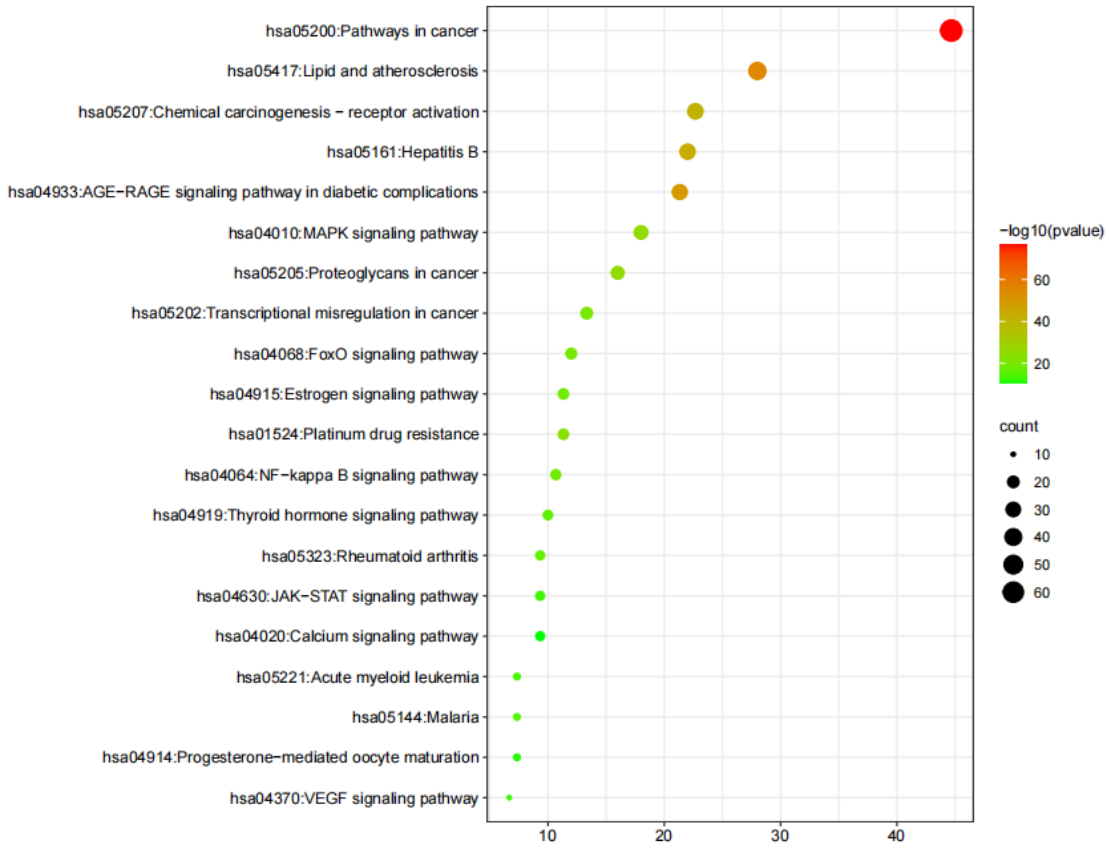

Figure 5. KEGG enrichment analysis diagram.

Table 4. Molecular docking information.

Target	Active Ingredient	Bindin Genergy /kcal·mol^{-1}
TP53	quercetin	−6.4
	kaempferol	−6.4
JUN	quercetin	−4.6
	kaempferol	−4.7

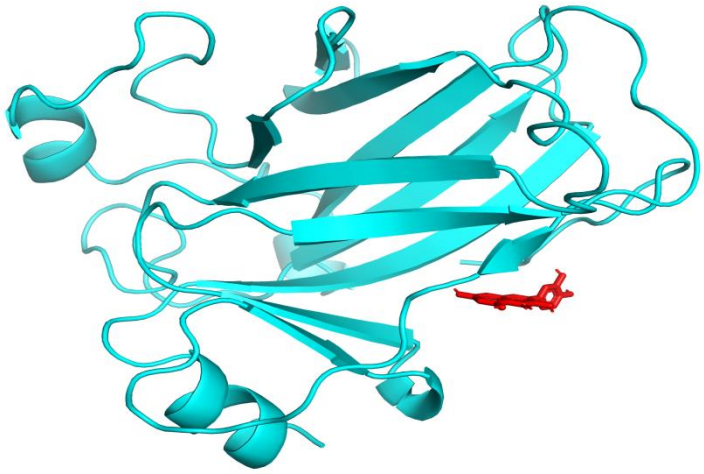

Figure 6. The docking diagram of TP53 and quercetin.

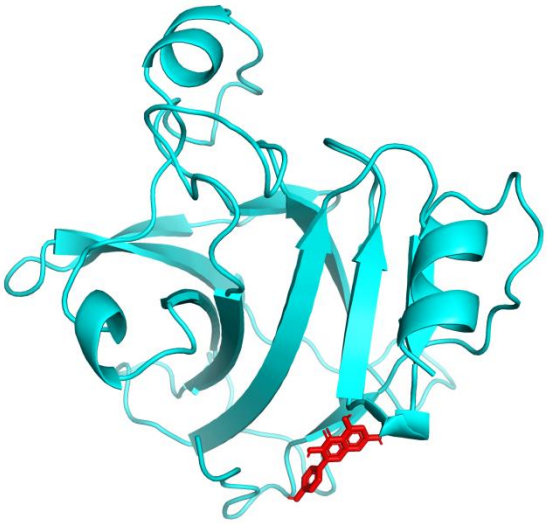

Figure 7. The docking diagram of TP53 and kaempferol.

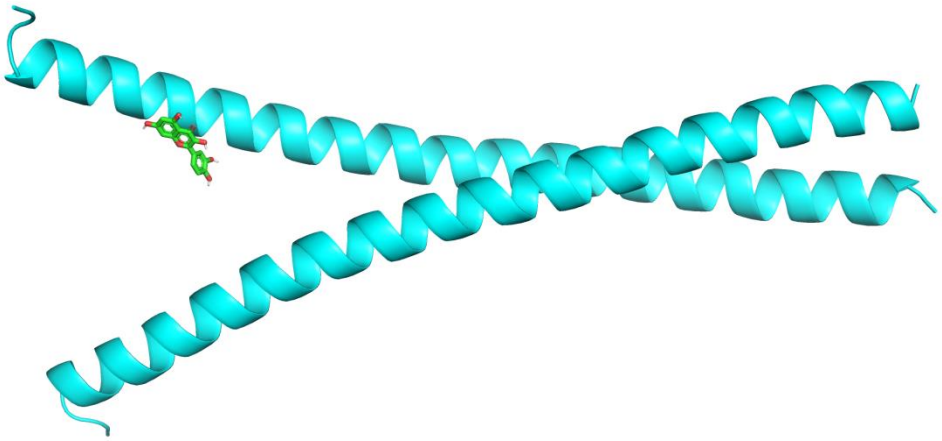

Figure 8. The docking diagram of JUN and quercetin.

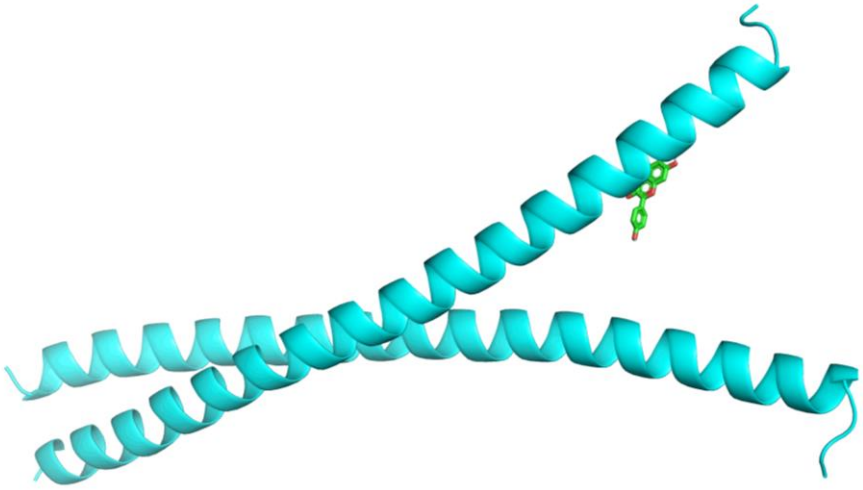

Figure 9. The docking diagram of JUN and kaempfero.

4. Discuss

Gastric cancer is a disease of digestive system, and it is also a disease with high molecular and phenotypic heterogeneity [22], with high morbidity and mortality. At present, the treatment methods of gastric cancer mainly include laparotomy therapy and laparoscopic

surgery [23], integrated traditional Chinese and Western medicine therapy [24], targeted therapy [25], immunotherapy of Traditional Chinese and Western Medicine, Radiotherapy and other methods [26]. In recent years, the adjuvant treatment of cancer by TRADITIONAL Chinese and Western medicine has received more and more attention. Galangal (Alpinia Officinarum Hance), a plant of the ginger family, has the functions of warming the stomach, antiemetic, dispelling cold and relieving pain [27]. Modern research has isolated a variety of effective pharmacological components from galangal, mainly volatile oils [28], flavonoids [29] and diarylheptanes [30]. These pharmacological effects have prominent effects in antibacterial [31], antioxidant [32], antiulcer, hypoglycemic [33], inhibiting tumor malignant proliferation [34] and anti-inflammatory analgesic [35] effects have a prominent role. However, the above studies have not fully elucidated the specific network regulatory role of galangal in gastric cancer.

It can be seen from the galangal-active ingredient-target-disease network diagram that the active ingredients closely related to gastric cancer are quercetin, kaempferol, β-sitosterol. Gao Lifeng et al. found that quercetin has inhibitory effects on a variety of tumor cells in the human body, including promoting apoptosis of tumor cells, inhibiting the growth, proliferation, and metastasis of tumor cells [36]. Quercetin has a significant killing effect on gastric cancer cells in vitro, and studies against apoptotic proteins have also shown that quercetin induces apoptosis in cells and weakens the activity of anti-apoptotic proteins [37]. Kaempferol can induce apoptosis of tumor cells through the mitochondrial apoptosis pathway, and can also induce apoptosis of gastric cancer cells by inhibiting extracellular signaling, and the protein kinase pathway [38]. Kaempferol can produce an antitumor effect by activating the TP53 pathway [39]. Ren Jing et al. found that the anti-cancer effect of isomerin is mainly reflected in the ability to inhibit the cell cycle, induce apoptosis, promote autophagy, inhibit its invasion and metastasis and enhance chemotherapy sensitivity [40]. In addition, studies have shown that isomyrin inhibits the migration invasion of tumor cells by raising HIF-1α levels [41]. Studies have shown that β-sitosterol can inhibit the proliferation and occurrence of tumor cells, inhibit the differentiation and proliferation of tumor cells, and induce apoptosis of tumor cells [42]. It can be seen that multiple active ingredients in galangal can play a role in treating stomach cancer.

The analysis of PPI maps, TP53, AKT1, JUN, etc. may be the key targets of galangal in the treatment of gastric cancer. TP53 is a tumor suppressor gene, is a transcription factor, can effectively control cell growth and trigger apoptosis, TP53 function in normal cells and tumors show diversification and participate in the mutual regulation of a variety of cell signal transduction pathways [43]. AKT has three homologous isomers and mutations in the AKT1, AKT2, AKT3, AKT1 gene loci play an important role in regulating tumor growth, proliferation, metabolism and other biological functions [44]. AKT1 and STMN1 proteins are highly expressed in gastric cancer tissues and can assist in the diagnosis and differential diagnosis of gastric cancer [45].

Enhanced transcriptional activity of JUN protein in gastric cancer tissue [46], meanwhile, JNK plays a key role in cell proliferation, apoptosis, and tumorigenesis, and the activation of the JNK signaling pathway is closely related to apoptosis [47]. KEGG enrichment results show that galangal has a therapeutic effect on gastric cancer through cancer pathways, MAPK signaling pathways and other related pathways. When activated, the MAPK signaling pathway has different effects on cell physiology, such as coordinated gene transcription, cell cycle control, and apoptosis [48]. MAPK signaling pathway affects tumor formation, development, metastasis, aggressiveness and drug resistance [49]. In order to further verify the therapeutic effect of galangal on gastric cancer, quercetin and kaempferol are docked with TP53 and JUN, and ligands and receptors can bind freely to each other.

In summary, the core components of galangal are quercetin, kaempferol, β-sitosterol, etc., which may act on core targets such as TPS3, AKTI, JUN through Pathways in cancer, Lipid and atherosclerosis, Hepatitis B, Chemical carcinogenesis-receptor activation, MAPK signaling pathway and play a role in treating gastric cancer. Therefore, galangal can act on

gastric cancer through multi-component, multi-target and multi-pathway, providing clues and ideas for further in-depth study of its mechanism of action.

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